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COMBINATION MEDICATION

[Kombinationsarzneimittel]

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[There are no amendments to this patent.]

The following data are taken from the documents submitted by the applicant.

Specification

Area of application of the invention

The invention concerns a new combination preparation for the treatment of chronic obstructive respiratory diseases.

Known technical background

The combination of selected glucocorticoids with certain  $\beta_2$ -sympathomimetics is described in various patent applications (e.g., EP 0 416 950, EP 0 416 951, WO93/11773).

Various new glucocorticoids are disclosed in DE-OS 41 29 535, also including the active substance ciclesonide.

### Description of the invention

The purpose of the present invention was to make available an antiasthmatic agent for local application that fulfills the following conditions.

- Good local (topical) action
- Lack of systematic (side) effects
- Low oral bioavailability
- Rapid abolition of the bronchospasm
- Good anti-inflammatory action
- Good suitability for long-term therapy
- Favorable influence on the bronchial hyperreactivity.

It was now found that the combined use of the active substance ciclesonide with a  $\beta_2$ -sympathomimetic meets the above conditions in an outstanding manner.

The subject of the invention is thus the combined use of ciclesonide with a  $\beta_2$ -sympathomimetic in the treatment of respiratory diseases.

In the sense of the present invention, not only is the epimer mixture understood by the active substance designation "ciclesonide." Rather, this designation also covers the pure epimers (thus the compounds (11 $\beta$ , 16 $\alpha$ )-16, 17((cyclohexyl methylene)bis(oxy))-11-hydroxy-21-(2-methyl-1-oxopropoxy)pregna-1,4-dien-3,20-dione and (11 $\beta$ , 16 $\alpha$  (S))-16,17((cyclohexyl methylene)bis(oxy))-11-hydroxy-21-(2-methyl-1-oxopropoxy)pregna-1,4-dien-3,20-dione as well as mixtures of these epimers with each other in any arbitrary mixing ratio. The use of ciclesonide consisting of essential parts of R-epimers is particularly preferred in this combined application.

In particular, selectively acting substances that have only a slight cardiac action and thus are also used in the treatment of bronchial asthma are mentioned as  $\beta_2$ -sympathomimetics. The following are named as appropriate  $\beta_2$ -sympathomimetics, for example: salbutamol, tulobuterol, terbutalin, carbutoleol, pirbuterol, isoxsuprin, reproterol, clenbuterol, fenoterol, bamethan, hexoprenalin, formoterol, salmeterol, picumeterol, rimiterol, procaterol, bambuterol, bitolterol, mabuterol, clorprenalin, isoetarin, etanterol, imoxiterol, naminterol, salmefamol and zinterol.

The  $\beta_2$ -sympathomimetics can be as is or in a chemically bound form. It is understood here that the  $\beta_2$ -sympathomimetics can also be in the form of their pharmacologically compatible salts and/or as solvates (e.g., hydrates), etc. The following are suitable in particular as pharmacologically compatible salts: water-soluble and water-insoluble acid addition salts with acids such as hydrochloric acid, bromohydracid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric

acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluene sulfonic acid, methane sulfonic acid or 1-hydroxy-2-naphthonic acid, where the acids in the salt production, depending on whether a monobasic or polybasic acid is involved and depending on which salt is desired, are used in equimolar quantitative ratio or one deviating from that. Furthermore, the said  $\beta_2$ -sympathomimetics can also be as pure enantiomers or as enantiomer mixtures in any mixing ratio. Due to the compatability of the dosing mixtures, the active substance formoterol and its salts, especially the fumarate, and in the form of the dehydrate, can be mentioned as the preferred  $\beta_2$ -sympathomimetic.

In particular, allergenically and inflammatorily induced bronchial diseases (bronchitis, obstructive bronchitis, spastic bronchitis, allergic bronchitis, allergic asthma, bronchial asthma), which can be treated with the invention combination also in the sense of a long-term therapy (if desired, with adaptation of the dosage of the individual components to the relevant requirements, e.g., due to seasonally conditioned fluctuations), are mentioned as respiratory diseases.

In the sense of the present invention, "use" is primarily understood as topical application in inhaled form. The substances are preferably administered by inhalation in the form of aerosols, where the aerosol particles of solid, liquid or mixed composition have a diameter of 0.5-10  $\mu\text{m}$ , advantageously 2-6  $\mu\text{m}$ .

Aerosol production can be made by pressure-driven nozzle atomizers or ultrasound atomizers, but advantageously by propellant-driven metering aerosols or the propellant-free use of micronized active substances from inhalation capsules.

The combined application in the sense of the present invention is to be understood such that the substances are applied by inhalation simultaneously from a device suitable for this. Atomizers, dosable propellant inhalers (metering aerosols) or powder inhalers (dry aerosol generators), etc. are mentioned as suitable devices. The substances can be ready-mixed or they can be taken simultaneously from separate packaging units in the inhalation, e.g., from two interconnected metering aerosols.

The use of two separate packaging units offers the advantage that the dose of ciclesonide on the one hand and of  $\beta_2$ -sympathomimetic on the other to be applied can be attuned to each other and adapted precisely to the individual case. This can occur, e.g., with the use of metering aerosols so that a precisely defined amount of the active substance is prepared per spray batch.

The combined use in the sense of the present invention can however also be understood so that the application of the individual components occurs immediately one after the other or also with a greater time interval, where the  $\beta_2$ -sympathomimetic is advantageously applied by inhalation first to relax the respiratory passages for the following application of ciclesonide to

assure a greater and more uniform deposition of ciclesonide in the respiratory passages and the lungs.

The metering of the active substance is done in an amount appropriate for the individual dosing, where the dosages with the combined administration of the active substance can be reduced relative to the norm due to the mutual positively influencing and enhancing individual actions. Ciclesonide is usually administered in a dosage of 0.05-1 mg daily, if desired, in the form of several, preferably two applications daily.  $\beta_2$ -sympathomimetic is administered (depending on intensity of action) in a dose of 0.002-0.5 mg daily, for example. The  $\beta_2$ -sympathomimetic formoterol preferred for the combination is administered in a dosage of 0.005 mg to 0.05 mg, especially from 0.01 to 0.03 mg daily.

Depending on the inhaler system used, the administration forms, besides the active substances, also contain the required adjuvants, e.g., propellant gases (e.g., Freon in metering aerosols), surface-active substances, emulsifiers, stabilizers, preservatives, flavors, fillers (e.g., lactose in powder inhalers) or possibly additional active substances.

A multiplicity of devices, with which aerosols of optimal particle size can be produced and applied by using an inhalation technique as patient-appropriate as possible are available for the purpose of inhalation. Besides the use of attachments (spacer, expander) and pear-shaped containers (e.g., Nebuato<sup>®</sup>, Volumatic<sup>®</sup> as well as automatic spray batch triggerings (Autohaler<sup>®</sup>) for metering aerosols, a series of technical solutions are available in the case of powder inhalers (e.g., Diskhaler<sup>®</sup>, Rotadisk<sup>®</sup>, Turbohaler<sup>®</sup> or the inhaler described in the European patent application EP 0 505 321), with which an optimal active substance application can be achieved.

## Examples

### 1. Metering aerosol

1.24 kg of trichlorofluoromethane (R 11) is weighed into a coolable autoclave and cooled to -30°C. Under continuous stirring, 10.2 g of sorbitol trioleate, 3.6 ciclesonide micronized and 7.2 g of salbutamol are metered in. Then 1.22 kg of cryofluoran (R 114) and 2.51 kg of dichlorodifluoromethane (R 12) are added with continued stirring. After the vessel is closed, the contents are dispersed for 10 min with an Ultra-turrax at a maximum rpm. 15.0 g of the suspension is filled through into the aerosol case by pressure filling. A spray batch contains 50 µg of ciclesonide and 100 µg of salbutamol.

### 2. Metering aerosol

As described in Example 1, 1.23 kg of trichlorofluoromethane (R 11), 11.0 g of sorbitan trioleate and 7.2 g of ciclesonide micronized, 7.2 g of salbutamol micronized, 1.22 kg of

cryofluoran and 2.51 kg of dichlorodifluoromethane (R 12) are dispersed and filled into an aerosol case. A spray batch contains 100 µg of ciclesonide and 100 µg of salbutamol.

### 3. Metering aerosol

As described in Example 1, 1.23 kg of trichlorofluoromethane (R 11), 12.0 g of sorbitan trioleate and 7.2 g of ciclesonide micronized, 14.4 g of hexoprenalin sulfate micronized, 1.22 kg of cryofluoran and 2.51 kg of dichlorodifluoromethane (R 12) are dispersed and filled into an aerosol case. A spray batch contains 100 µg of ciclesonide and 200 µg of hexoprenalin sulfate.

### 4. Metering aerosol

As described in Example 1, 1.99 kg of trichlorofluoromethane (R 11), 15.5 g of sorbitan trioleate and 3.7 g of ciclesonide micronized, 1.1 g of formoterol fumarate dehydrate ( $\Delta$  0.86 g of formoterol) micronized and 3.00 kg of dichlorodifluoromethane (R 12) are dispersed and filled into an aerosol case. A spray batch contains 50 µg of ciclesonide and 12 µg of formoterol.

### 5. Metering aerosol

400 mg of ciclesonide micronized, 482 mg of salbutamol sulfate micronized ( $\Delta$  400 mg of salbutamol) and 36.1 g of lactose monohydrate Ph. Eur. II are mixed in two portions in a Turbula mixer. The mixture screened through a 0.71 mm sieve is transferred into the mixing container of a planetary mixer. After mixing in an additional 63.0 g of lactose monohydrate Ph. Eur. II, 25 mg of the powder mixture is filled into capsules of size 3, which can be applied with a commercial powder inhaler. A spray batch contains 100 µg of ciclesonide and 100 µg of salbutamol.

## Claims

1. Medication containing the active substance ciclesonide and a  $\beta_2$ -sympathomimetic in fixed or free combination.

3. Medication for the treatment of respiratory diseases, containing the active substance ciclesonide and a  $\beta_2$ -sympathomimetic in fixed or free combination and together with the usual adjuvant or vehicle substances in an administration form suitable for inhalation application.

3. Medication according to Claim 2, characterized in that the active substance ciclesonide and the  $\beta_2$ -sympathomimetic are ready-mixed in a fixed combination.

4. Medication according to Claim 2, characterized in that the active substance ciclesonide and the  $\beta_2$ -sympathomimetic are in separate packaging units, where the active substance ciclesonide and the  $\beta_2$ -sympathomimetic can be taken from the separate packaging units so that they are available for the simultaneous application by inhalation.

5. Medication according to Claim 2, characterized in that the active substance ciclesonide and the  $\beta_2$ -sympathomimetic are in separate packaging units, where the active substance ciclesonide and the  $\beta_2$ -sympathomimetic are taken from separate packaging units so that they are applied one after the other by inhalation.

6. Medication according to Claim 2, characterized in that the active substance ciclesonide is present to more than 95% in the form of its R-epimers.

7. Medication according to Claim 2, characterized in that the active substance ciclesonide is present to more than 95% in the form of its R-epimers and that the active substance formoterol or a salt and/or hydrate of this active substance is involved in the case of  $\beta_2$ -sympathomimetic.

8. Use of the active substance ciclesonide in fixed or free combination with a  $\beta_2$ -sympathomimetic in the treatment of respiratory diseases.

9. Use according to Claim 8, characterized in that the active substance ciclesonide is present to more than 95% in the form of its R-epimers.

10. Use according to Claim 8, characterized in that the active substance ciclesonide is present to more than 95% in the form of its R-epimers and that the active substance formoterol or a salt and/or hydrate of this active substance is involved in the case of the  $\beta_2$ -sympathomimetic.